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09/902,713	07/10/2001	Avi Ashkenazi	10466/71	1320

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EXAMINER	
ROARK, JESSICA H	
ART UNIT	**PAPER NUMBER**
1644	

DATE MAILED: 10/01/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/902,713	Applicant(s) ASHKENAZI ET AL.	
	Examiner Jessica H. Roark	Art Unit 1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 July 2001 and 27 August 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *39-44* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *39-44* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *10 July 2001* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☒ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *9* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Applicant's amendments, filed 7/10/01 and 8/27/02 (Paper Nos. 5 and 10), are acknowledged.
Claims 1-38 have been canceled.
Claims 39-44 have been added.
Claims 39-44 *are pending.*

Sequence Compliance

2. Sequence compliance: The instant application appears to be in sequence compliance for patent applications containing nucleotide sequence and/or amino acid sequence disclosures.

Drawings

3. Formal drawings have been submitted which fail to comply with 37 CFR 1.84.
Please see the enclosed form PTO-948.

INFORMATION ON HOW TO EFFECT DRAWING CHANGES

A. Correction of Informalities -- 37 CFR 1.85

New corrected drawings must be filed with the changes incorporated therein. Identifying indicia, if provided, should include the title of the invention, inventor's name, and application number, or docket number (if any) if an application number has not been assigned to the application. If this information is provided, it must be placed on the front of each sheet and centered within the top margin. The drawings should be filed as a separate paper with a transmittal letter addressed to the Official Draftsperson.

B. Corrections other than Informalities Noted by Draftsperson on form PTO-948.

All changes to the drawings, other than informalities noted by the Draftsperson, MUST be made in the same manner as above except that, normally, a highlighted (preferably red ink) sketch of the changes to be incorporated into the new drawings MUST be approved by the examiner before the application will be allowed. No changes will be permitted to be made, other than correction of informalities, unless the examiner has approved the proposed changes.

Timing of Corrections

Applicant is required to submit acceptable corrected drawings within the time period set in the Office action. See 37 CFR 1.185(a). Failure to take corrective action within the set (or extended) period will result in ABANDONMENT of the application.

Oath

4. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because: non-initialed and non-dated alterations have been made to the oath or declaration. See 37 CFR 1.52(c).

See in particular the residence information for Wei-Qiang Gao.

Priority

5. According to the priority statement filed 8/27/02, priority for the instant application is claimed to USSN 09/665,350 (9/18/00), which is a CON of PCT/US00/04414 (2/22/00), which is a CIP of PCT/US00/03565 (2/11/00) which is a CIP of PCT/US98/19330 (9/16/98) which claims priority to provisional application 60/063,045 (10/24/97).

A) Based on the information given by applicant and an inspection of the patent applications, the examiner has concluded that the subject matter defined in this application is supported by the disclosure in USSN 09/902,713, filed 7/10/01, but is not supported by any of the others because the instant subject matter lacks the necessary support under 35 USC 112, first paragraph, as set forth below. Accordingly, the subject matter defined in claims 39-44 appears to have an effective filing date of 7/10/01.

Should the applicant disagree with the examiner's factual determination above, it is incumbent upon the applicant to provide the serial number and specific page number(s) of any parent application filed prior to 7/17/01 which specifically supports the particular claim limitation for each and every claim limitation in all the pending claims which applicant considers to have been in possession of and fully enabled for prior to 7/17/01.

B) In addition, Applicant is reminded that the status of nonprovisional parent applications (whether patented or abandoned) should also be included in the priority claim If a parent application has become abandoned, the expression "now abandoned" should follow the filing date of the parent application.

IDS

6. The information disclosure statement filed 3/22/02 fails to comply with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609 because: the sequence alignments provided fail to provide any of the relevant information with respect to publisher, author (if any), title, relevant pages of the publication, date, and place of publication with respect to the sequences compared.

Title

7. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention *to which the claims are directed.*

The following new Title is suggested: ANTIBODIES TO PRO269 POLYPEPTIDES.

Specification

8. The disclosure is objected to because it contains an embedded hyperlink. See for example page 69 at line 8, page 71 at line 28, and page 146 at line 32. Applicant is required to delete the embedded hyperlink. See MPEP § 608.01. *Applicant is requested to carefully review the specification for any additional hyperlinks or other forms of browser executable code and delete them.*

9. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which Applicant may become aware in the specification.
Applicant is requested to update the ATCC address disclosed on page 250 to reflect the ATCC's current address: American Type Culture Collection, 10801 University Boulevard, Manassas, VA 20110-2209.

Claim Objections

10. Claim 43 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim, claim 39. Applicant is required to cancel the claim, or amend the claim to place the claim in proper dependent form, or rewrite the claim in independent form.

The specification does not appear to disclose that an antibody encompasses a labeled antibody (see definitions of an "antibody" on page 73 of the specification). Therefore, the inclusion of the limitation that the antibody is labeled in claim 43 broadens, rather than narrows, the scope of claim 39. It is suggested that Applicant rewrite the claim in independent form.

Claim Rejections - 35 USC § 101

11. 35 U.S.C. § 101 reads as follows:

> *"Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title".*

12. Claims 39-44 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a credible, specific and substantial asserted utility or a well established utility.

The specification asserts that PRO269 antibodies are useful for affinity purification of the PRO269 polypeptide (page 147 at lines 7-13). *However, utility for purification of a protein requires that the protein itself have a credible specific and substantial, or well established, utility.*

First, it is noted that there is no well-established utility for the PRO269 antibodies or polypeptide on record or of which the Examiner is aware.

With respect to the asserted utility of the PRO269 antibodies for purification of the PRO269 protein, the following points "A"-"B" are noted with respect to the PRO269 protein:

A) Asserted Utility of protein based on homology to thrombomodulin:
The instant specification discloses that the PRO269 polypeptide of SEQ ID NO:96, encoded by residues 314 to 1783 of SEQ ID NO:95 shown in Figure 35, has "significant" homology to urinary thrombomodulin and various thrombomodulin analogues (e.g., specification page 103, lines 4-13).

The specification on page 12 at line 30 to page 13 at line 1 discloses that thrombomodulin is a natural anticoagulant that has a possible therapeutic use an antithrombotic agent with reduced risk for hemorrhage as compared with heparin.

Based upon the homology of PRO269 to thrombomodulin, the specification asserts that PRO269 is a new member of the thrombomodulin family (e.g., specification page 103, lines 4-13). The specification further asserts that PRO269, like thrombomodulin, may also be useful as an antithrombotic agent with reduced risk for hemorrhage as compared with heparin (e.g., page 132 at line 38 to page 133 at line 3).

In the instant case, Applicant does not provide an alignment of either the DNA or protein sequences to the DNA or protein sequence of thrombomodulin. Alignment of the PRO269 protein (SEQ ID NO:96) over its full length (i.e., residues 1-490) to human thrombomodulin provides a query match of only 8.7%, with a best local similarity of 25.7% over residues 16-286 (see attached alignments "A" and "B").

However, other proteins not related to thrombomodulin in function also share a level of homology to PRO269 similar to that shared by PRO269 and thrombomodulin. For example, Tenner et al. (U.S. Pat. No. 5,965,439) teach the cell surface protein C1qRp (SEQ ID NO:2 of Tenner et al.). Alignment of PRO269 (instant SEQ ID NO:96) and C1qRp (SEQ ID NO:2 of Tenner et al.) produces a query match of 11.8% and a best local similarity of 21.4% over residues 1-451 of instant SEQ ID NO:96 (see attached alignment "C"). C1qRp is taught by Tenner et al. to function in host defense by functioning as the receptor for the complement component C1q (see entire document, e.g., columns 1-2 "Introduction" and "Summary of the Invention"). Tenner et al. also note at column 35, lines 55-60 that diverse, non-related extracellular proteins show some homology to one another due to the sharing of EGF domains; thus explaining the low level of homology of PRO269 to both thrombomodulin and C1qRp.

Generally, the art acknowledges that function cannot be predicted based solely on structural similarity to a protein found in the sequence databases. For example, Skolnick et al. (2000, Trends in Biotech. 18:34-39) state that knowing the protein structure by itself is insufficient to annotate a number of functional classes, and is also insufficient for annotating the specific details of protein function (see Box 2, p. 36). Similarly, Bork (2000, Genome Research 10:398-400) states that the error rate of functional annotations in the sequence database is considerable, making it even more difficult to infer correct function from a structural comparison of a new sequence with a sequence database (see especially p. 399). Such concerns are also echoed by Doerks et al. (1998, Trends in Genetics 14:248-250) who state that (1) functional information is only partially annotated in the database, ignoring multi functionality, resulting in underpredictions of functionality of a new protein and (2) overpredictions of functionality occur because structural similarity often does not necessarily coincide with functional similarity. Smith et al. (1997, Nature Biotechnology 15:1222-1223) remark that there are numerous cases in which proteins having very different functions share structural similarity due to evolution from a common ancestral gene. Brenner (1999, Trends in Genetics 15:132-133) argues that accurate inference of function from homology must be a difficult problem since, assuming there are only about 1000 major gene superfamilies in nature, then most homologs must have different molecular and cellular functions. Bork et al. (1996, Trends in Genetics 12:425-427) add that the software robots that assign functions to new proteins often assign a function to a whole new protein based on structural similarity of a small domain of the new protein to a small domain of a known protein. Such questionable interpretations are written into the sequence database and are then considered facts. Finally, Bowie et al. (1990, Science 247:1306-1310) state that determination of three dimensional structure from primary amino acid sequence, and the subsequent inference of detailed aspects of function from structure is extremely complex and unlikely to be solved in the near future (p. 1306).

The homology of PRO269 to thrombomodulin is so low and indistinct compared to other proteins having diverse functions that the ordinary artisan cannot consider it more likely than not that PRO269 is a member of the thrombomodulin family, or that PRO269 has the same function as thrombomodulin based upon the homology of the PRO269 polypeptide to thrombomodulin. The presence of an EGF domain in both PRO269 and thrombomodulin is sufficient to explain the homology results; but as suggested by Bork et al. supra, the sharing of a small domain does not establish that this new protein shares any function with thrombomodulin.

The specification therefore fails to support the asserted specific and substantial utility of the PRO269 polypeptide as an antithrombotic agent with reduced risk for hemorrhage as compared with heparin.

B) Asserted Utility of protein based upon "positive" results in certain disclosed assays:
The specification asserts that the PRO269 nucleic acid of SEQ ID NO:95/ATCC Deposit #209397 can be used to express the PRO269 polypeptide, which can itself be used:

i) as an antithrombotic agent (e.g., page 132 at line 38 to page 133 at line 3);
ii) to enhance an immune response (e.g., page 208 at lines 29-30);
iii) to treat cardiac disorders associated with cardiac hypertrophy (e.g., page 214 at lines 6-8);
iv) to treat nervous system disorders where neuronal proliferation would be beneficial (e.g., page 216 at lines 31-32);
v) to treat any disorder where stimulation or inhibition of glucose uptake by skeletal muscle would be beneficial (e.g., page 217 at lines 20-22); and
vi) to provide antibodies that would be useful in tumor therapy (page 234, lines 1-3).

Thus the specification discloses that the polypeptide PRO269 is associated with several testable in vitro functions. However, while the utilities asserted to be associated with each assay in which the PRO269 polypeptide is positive appear to be specific and substantial; it is not credible based upon the information of record that a positive reaction in the disclosed assays provides sufficient support such that the skilled artisan would consider it more likely than not that the PRO269 polypeptide would in fact have the utility asserted with respect to any one or more of the assays in which PRO269 is positive.

Anti-thrombotic:
The asserted use of the PRO269 polypeptide as an anti-thrombotic is based upon a low level of homology of PRO269 to the anti-thrombotic thrombomodulin (see e.g., pages 132-133). As discussed in detail supra, the state of the art did not recognize that the low level of homology of PRO269 to thrombomodulin was sufficient to suggest that the ordinary artisan would consider it more likely than not that PRO269 shared functionality with thrombomodulin (please see supra for supporting evidence regarding the lack of predictability of protein function based on homology). Applicant provides no supporting evidence that any functional domains are present in the PRO269 polypeptide that would suggest that the skilled artisan would consider it more likely that not that a polypeptide with this structure would possess of anti-thrombotic activity (e.g., binding of thrombin or activation of Protein C, see Esmon's review of thrombomodulin's activity in The FASEB J. 1995; 9:946-955). Thus the utility asserted based upon homology to thrombomodulin is not credible based upon the information of record.

Immune response stimulator:
The asserted use of the PRO269 polypeptide as an immune response stimulator is based upon its activity in a mixed lymphocyte reaction (see Example 74, pages 208-209). However, the specification does not demonstrate that PRO269 can directly stimulate lymphocytes (i.e., function by itself to stimulate lymphocytes). Neither is it apparent that the skilled artisan would consider it more likely than not that a protein that stimulated a mixed lymphocyte reaction to some undisclosed degree could be used to stimulate an immune response. For example, no evidence is of record that the control CD4Ig protein can stimulate an immune response; thus the utility asserted based upon this assay is not credible based upon the information of record.

Treatment of cardiac disorders associated with cardiac hypertrophy:
The asserted use of the PRO269 polypeptide for treatment of disorders associated with cardiac hypertrophy is based upon its ability to inhibit adult heart hypertrophy in an in vitro assay utilizing isolated myocytes (see Example 83, page 214). However, the record does not establish that this in vitro assay by itself would lead the skilled artisan to consider it more likely than not that a protein positive in the assay can be used for the asserted utility of treating cardiac disorders associated with cardiac hypertrophy. For example, the art teaches the use of the in vitro assay *in conjunction with* in vivo assays of cardiac hypertrophy and notes that it is the in vivo assays that provide valuable information about the therapeutic potential of a new agent (see for example Jin et al. in U.S. Patent No. 6,187,304, entire document but especially the discussion of assays at columns 10-11 and the comment regarding the value of the in vivo assay at column 11, lines 17-19).

It is also noted that the PRO269 protein was not disclosed to be positive in what appears to be a related assay of inhibition of neonatal (rather than adult) heart hypertrophy (Example 100, page 237). Thus the utility asserted based upon this assay is not credible based upon the information of record.

Treatment of nervous system disorders where neuronal proliferation would be beneficial:
The asserted use of the PRO269 polypeptide for treatment of nervous system disorders where neuronal proliferation would be beneficial is based upon the ability of PRO269 to induce c-fos in cortical neurons in vitro (see Example 87, pages 216-217). However, the record does not establish that this in vitro assay by itself would lead the skilled artisan to consider it more likely than not that a protein positive in the assay can be used for the asserted utility of treating any nervous system disorder. Besides the general art-recognized difficulties associated with treatment of nervous system disorders in general, Herdegen et al. (Oncogene 2001; 20:2424-2437) review that the role of c-fos, the protein disclosed to be induced by PRO269, is far from clear and that c-fos, although promiscuously expressed following a variety of stimuli, is often associated with neurodegenerative events (see entire document, but especially the comments on page2425 "c-fos", page 2430 "c-fos/ERK-axis" and page 2432 "The promiscuous expression of the c-fos protein..."). The disclosure that PRO269 induces c-fos in cortical neurons does not appear to be consistent with therapeutic treatment of nervous system disorders where neuronal proliferation would be beneficial. The utility asserted based upon this assay is therefore not credible based upon the information of record.

Treatment of disorders where stimulation or inhibition of glucose/FFA uptake would be beneficial:
The asserted use of the PRO269 polypeptide for treatment of any disorder where stimulation or inhibition of glucose/FFA uptake by skeletal muscle would be beneficial is based upon the ability of PRO269 to have some effect (either stimulatory or inhibitory) on glucose and/or FFA uptake by skeletal muscle in response to insulin in vitro (see Example 89, page 217). It is noted that the disclosure does not indicate whether the effect of the PRO269 polypeptide is stimulatory or inhibitory. However, even were the nature of the effect disclosed, the record still does not establish that this in vitro assay by itself would lead the skilled artisan to consider it more likely than not that a protein positive (either stimulatory or inhibitory) in the assay can be used for the asserted utility of treating any particular disorder associated with stimulation or inhibition of glucose and/or FFA uptake. Based upon the information of record, the utility asserted based upon this assay is therefore not credible.

Tumor therapy:
The asserted use of the PRO269 polypeptide for tumor therapy is based on the preparation of antibodies to PRO269 and their use as antagonists of the PRO269 polypeptide (see e.g., page 235, lines 1-3 in view of the DNA amplification results on pages 222-234). However, given the results on page 230-234, there does not appear to be a particular tumor type that is associated with PRO269. Even were PRO269 an established target on tumors or a subclass of tumors, the skilled artisan still would not consider it more likely than not that an antibody antagonist of PRO269 could be used as a tumor therapeutic (e.g., see Dillman in J. Clin. Oncol. 1994; 12:1497-1515). The utility asserted based upon this assay is therefore not credible based upon the information of record.

The skilled artisan also would not view the asserted utilities for the PRO269 protein as credible because there is no indication of the extent of stimulation (i.e., how does the stimulation induced by PRO269 compare to that of the positive control) and the relevance of the positive control (i.e., does the positive control itself have the asserted utility).

Thus none of the utilities asserted for the PRO269 polypeptide appear to be credible specific and substantial, or well established, utilities.

In view of the apparent lack of a credible specific and substantial, or well established, utility for the PRO269 polypeptide; antibodies to PRO269 also appear to lack credible specific and substantial, or well established, utility based solely on a use in affinity purifying the polypeptide.

Asserted Utilities of Antibodies, other than for protein purification:

The specification also asserts on pages 146-147 that antibodies to PRO269 can be used for diagnostic applications in which the antibody is used to detect the polypeptide. The specification on page 130 at lines 3-6 asserts that antibodies of PRO269 can be used as antagonists of PRO269 protein function.

However, no disease association appears to have been provided for the PRO269 polypeptides for the reasons set forth supra. Although PRO269 can be found in certain tumors by amplification, the relevance of this observation remains to be determined and it is not readily apparent that a correlation with any one tumor type exists such that antibodies to PRO269 could be used diagnostically or therapeutically. Although in some instances antibodies to a polypeptide may have utility even though the function of the protein is unknown, there does not appear to be any evidence of record to indicate that the instant antibodies to PRO269 have credible specific and substantial, or well established, utilities that do not require knowledge of PRO269's function.

Applicant is invited to make of record objective evidence supporting the asserted utilities.

However, at present the instant disclosure fails to clearly establish how one of skill in the art could use the claimed invention in a way that constitutes a credible specific and substantial utility. The disclosed uses appear only to provide starting points for further research and investigation into potential practical uses of the claimed PRO269 polypeptide. "Congress intended that no patent be granted on a chemical compound whose sole 'utility' consists of its potential role as an object of use-testing." Brenner v. Manson, 148 USPQ 689 (1966) at 696.

Applicant is directed to the Utility Examination Guidelines, Federal Register, Vol. 66, No. 4, pages 1092-1099, Friday January 5, 2001.

Claim Rejections - 35 USC § 112

13. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

14. Claims 39-44 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a credible specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

15. Antibodies to the PRO269 polypeptide do not appear to be enabled for the reasons set forth supra. However, even were sufficient objective evidence provided that an antibody to PRO269 were enabled for one or more of the asserted uses, the following rejections would still apply:

Claims 39-44 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is undue include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

Besides protein purification, the specification also asserts on pages 146-147 that antibodies to PRO269 may be used as diagnostic reagents, and asserts on page 130 at lines 3-6 that antibodies to PRO269 may be used as antagonists of PRO269 function.

The state of the art recognized that antibodies could be used in diagnostic and protein antagonist applications in general, and the level of skill in the art is high. However, the use of an antibody to PRO269 as either a diagnostic reagent or a therapeutic antagonist requires guidance as to which conditions are associated with the PRO269 polypeptide. Although the specification has disclosed certain functions of the PRO269 protein in vitro, as discussed supra the connection between these in vitro activities and any particular disease is unclear. Further, although the specification asserts that antibodies can be used as antagonists of PRO269 function, there does not appear to be sufficient guidance as to how to use the antibody antagonist in any particular condition.

For example, the specification discloses on pages 208-209 that the PRO269 polypeptide stimulates an in vitro mixed lymphocyte reaction. The specification asserts that the PRO269 polypeptide can be used to enhance immune responses (e.g., page 208, lines 29-30). The specification also asserts that a therapeutic agent may take the form of antibody antagonists against the PRO269 polypeptide (e.g., page 208 at line 30-32). However, the specification does not set forth any conditions in which application of the antibody antagonist would be therapeutic. Thus in order to use the anti-PRO269 antibody as an antagonist, the skilled artisan would clearly have to conduct extensive an undue experimentation to identify relevant conditions.

Diagnostic applications also require guidance that the protein detected is either differentially expressed or overexpressed in a particular condition. However, the specification does not appear to establish the expression patterns of the PRO269 polypeptide, except in certain tumor lines (pages 222-234). Thus undue experimentation of the skilled artisan would be required to identify conditions in which expression of PRO269 was altered so that an anti-PRO269 antibody could be used diagnostically. Even with respect to the expression in tumor cells, it is unclear based on the evidence of record that PRO269 is expressed in a manner that is diagnostic of any particular tumor type or of cellular transformation.

Thus given the absence of working examples and the insufficient guidance with respect to situations in which the skilled artisan could use the PRO269 antibody; it would require extensive and undue experimentation to of the skilled artisan to use the instant PRO269 antibodies.

16. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

17. Claims 39-44 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Regarding claims 39 and 44, absent a definition of "specific binding" it is not clear what the difference between the two claims is and what each claim is meant to encompass, given that antibody binding is determined by the variable regions structure and is necessarily "specific".

Applicant is reminded that any amendment must point to a basis in the specification so as not to add new matter. See MPEP 714.02 and 2163.06.

35 U.S.C. §§ 102 and 103

18. The following rejections under 35 U.S.C. § 102 are made under the assumption that the effective filing date for the instantly claimed invention is 7/10/01, which is the actual filing date of the instant application.

Given the uncertainty associated with the effective filing date of the instant claims, certain rejections have been set forth in the alternative under more than one paragraph of 35 U.S.C. 102 until the effective filing date of the claims can be established.

Claim Rejections – 35 U.S.C. §§ 102 and 103

19. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

20. Claims 39-44 are rejected under 35 U.S.C. 102(b), *or in the alternative under 35 U.S.C. 102(a)*, as being anticipated by Wood et al. (WO 99/14328, see pages 1, 12, 39, 56, 72, 83-85, 92-98, 101, 108-112, 126-127, 185-187, Figures 35 and 36), as evidenced by the attached alignments "D".

Wood et al. teach an isolated PRO269 polypeptide having 100% amino acid sequence identity to SEQ ID NO:96 as shown in Figure 36 of the instant application, as evidenced by the attached alignment.

Wood et al. also teach antibodies to the PRO269 polypeptide (see especially pages 108-111). The antibodies of Wood et al. inherently "specifically bind" the polypeptide of SEQ ID NO:96, since as noted supra antibody binding is determined by the variable regions structure and is necessarily "specific".

Wood et al. teach that forms of the antibodies include monoclonal (e.g., page 108, especially lines 32-33) and humanized (e.g., page 110, especially lines 1-16).

Wood et al. also teach antibody fragments (e.g. page 110, especially lines 11-12).

Finally, Wood et al. teach antibodies that are labeled (see e.g., page 112, especially lines 6-13).

Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitation of specific binding would be an inherent property of the referenced antibodies.

The reference teachings thus anticipate the instant claimed invention.

21. Claims 39-44 are rejected under 35 U.S.C. 102(b) as being anticipated by Valenzuela et al. (WO 00/11015, see pages 1-2, 115-118, 167-168, 171-176, 183-184, 207-209 and pages 68-70 of the sequence listing), as evidenced by the attached alignment "E".

Valenzuela et al. teach an isolated vp15_1 polypeptide having 100% amino acid sequence identity to SEQ ID NO:96 as shown in Figure 36 of the instant application, as evidenced by the attached alignment.

Valenzuela et al. also teach antibodies to the vp15_1 polypeptide (see especially pages 207-209). The antibodies of Valenzuela et al. inherently "specifically bind" the polypeptide of SEQ ID NO:96, since as noted supra antibody binding is determined by the variable regions structure and is necessarily "specific".

Valenzuela et al. teach that forms of the antibodies include monoclonal and humanized antibodies (e.g., page 207, especially lines 29-33).

Valenzuela et al. also teach antibody fragments (e.g. page 208, especially lines 10-15).

Finally, Valenzuela et al. teach antibodies that are "diagnostic agents", therefore, Valenzuela et al. teach antibodies that are necessarily labeled either directly or indirectly to permit their detection (see e.g., page 208, especially lines 29-30).

Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitation of specific binding would be an inherent property of the referenced antibodies.

The reference teachings thus anticipate the instant claimed invention.

22. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> *(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.*

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

23. Claims 39 and 43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Valenzuela et al. (WO 00/11015, see pages 1-2, 115-118, 167-168, 171-176, 183-184, 207-209 and pages 68-70 of the sequence listing), as evidenced by the attached alignment "E", in view of Ramakrishnan et al. (US Pat. No. 5,817,310).

The claims are drawn to an antibody that binds to the polypeptide of SEQ ID NO:96, wherein the antibody is labeled.

Valenzuela et al. have been discussed supra and teach an antibody that binds to the polypeptide of SEQ ID NO:96, wherein the antibody is a diagnostic agent.

Valenzuela et al. do not explicitly state that the antibody that is a diagnostic agent is a labeled antibody.

Ramakrishnan et al. teach that labeling of antibodies for use in various diagnostic applications (e.g., column 17, especially lines 1-33).

Therefore, it would have been obvious to the ordinary artisan at the time the invention was made to label the antibody of Valenzuela et al. using any of a number of art-recognized labels as taught by Ramakrishnan et al. The ordinary artisan would have been motivated to label the antibodies of Valenzuela et al. in order to provide a variety of detection agents that could be used in diagnostic assays as taught by Valenzuela et al. Given the art-recognized methods for labeling antibodies for diagnostic applications, as taught by Ramakrishnan, the ordinary artisan at the time the invention was made would clearly have had a reasonable expectation of producing label versions of the antibodies of Valenzuela et al. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Conclusion

24. No claims are allowed.

25. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jessica H. Roark, whose telephone number is (703) 605-1209. The examiner can normally be reached Monday to Friday, 8:00 to 4:30. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached at (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

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